PROFESSIONAL INFORMATION FOR

PRAZOLOC 20 and PRAZOLOC 40

SCHEDULING STATUS

S4

PROPRIETARY NAME (AND DOSAGE FORM)

PRAZOLOC 20 (Enteric-coated tablets)

PRAZOLOC 40 (Enteric-coated tablets)

COMPOSITION

PRAZOLOC 20: Each enteric-coated tablet contains pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole

PRAZOLOC 40: Each enteric-coated tablet contains pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole

Inactive ingredients are calcium stearate, crospovidone, ferric oxide (yellow), hydroxypropyl cellulose, hypromellose, mannitol, methacrylic acid copolymer, propylene glycol, sodium carbonate, titanium dioxide, and triethyl citrate.

PRAZOLOC 20: contains sugar (mannitol) 49,145 mg per tablet

PRAZOLOC 40: contains sugar (mannitol) 98,290 mg per tablet

PHARMACOLOGICAL CLASSIFICATION

A 11.4.3 Medicine acting on the gastro-intestinal tract - Other.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Pantoprazole is a proton pump inhibitor, which inhibits specifically and dose proportionally, gastric H^+,K^+-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

Pantoprazole is a substituted benzimidazole which accumulates in the acidic compartment of the parietal cells after absorption. In the parietal cell it is protonated and chemically rearranged to the active inhibitor, a cyclic sulphenamide, which binds to the H^+,K^+-ATPase, thus inhibiting the proton pump and causing suppression of stimulated and basal gastric acid secretion after single oral pantoprazole dosing. Because pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus.

Pantoprazole exerts its full effect in a strongly acidic environment (pH < 3) and remains mostly inactive at higher pH values, which explains its selectivity for the acid secreting parietal cells of the stomach.

Therefore the complete pharmacological and therapeutic effect for pantoprazole can only be achieved in the acid secreting parietal cells. By means of a feedback

mechanism the effect is diminished at the same rate as acid secretion is inhibited.

Effect on gastric acid secretion:

Following oral administration, pantoprazole inhibits the pentagastrin stimulated gastric acid secretion. The mean acid inhibition was 85 %, 2½ to 3½ hours after dosing with pantoprazole 40 mg/day for 7 days.

After stopping the administration of pantoprazole, there is no evidence of rebound hypersecretion and 7 days after administering the last dose the acid output is normal.

Pantoprazole maintains the physiological pH-rhythm. The values, however, are shifted to higher levels. During the night, periods with pH values approximating placebo have been found to occur.

Although pantoprazole has a half-life of approximately 1 hour, the antisecretory effect increases during repeated once daily administration, demonstrating that the duration of action markedly exceeds the serum elimination half-life.

Pharmacokinetic properties

Absorption and distribution:

Pantoprazole is administered orally in the form of an enteric-coated tablet. Pantoprazole is unstable in acid. Since an acidic pH in the parietal cell acid canaliculi is required for activation, and since food stimulates acid production, pantoprazole should be taken about 30 minutes before meals.

Absorption takes place in the small intestine. Concurrent administration of food may somewhat reduce the rate of absorption of proton pump inhibitors. Concomitant use of other medicines that inhibits acid secretion, such as H_2-receptor antagonists, might be predicted to lessen the effectiveness of the proton pump inhibitors, such as pantoprazole.

On average, the maximum serum/plasma concentrations are approximately 2 to 3 µg/mℓ about 2½ hours after administration of 40 mg pantoprazole daily, as a single or multiple dose. The absolute systemic bioavailability of pantoprazole from single and multiple oral doses of pantoprazole is approximately 77 %.

The plasma kinetics for pantoprazole after oral administration is linear over the dose range 10 – 80 mg.

Metabolism:

Pantoprazole is almost exclusively metabolised in the liver. The main metabolite is desmethylpantoprazole, which is conjugated with sulphate.

Elimination:

Renal elimination represents the most important route of excretion (approximately 80 %) for the metabolites of pantoprazole. The balance is excreted with the faeces. The half-life of the main metabolite is approximately 1½ hours which is slightly longer than that of pantoprazole.

Pharmacokinetic profile in patients with impaired liver or renal function:

For patients with mild to moderate hepatic cirrhosis the elimination half-life values increase to between 7 to 9 hours. The AUC values increase by a factor of 5 to 8, while the maximum serum concentration only increases by a factor of 1,5 in comparison with healthy subjects.

In patients with renal impairment the half-life of the main metabolite is moderately increased but there is no accumulation at therapeutic doses. The half-life of pantoprazole in patients with renal impairment is comparable to the half-life of pantoprazole in healthy subjects. Pantoprazole is poorly dialysed.

A slight increase in AUC and C_{max} occurs in elderly volunteers compared with younger people.

INDICATIONS

PRAZOLOC 20 is indicated in the following:

- For the symptomatic improvement (e.g. heartburn, acid regurgitation, pain on swallowing) and healing of mild gastro-oesophageal reflux disease (GORD).
- In patients with healed reflux disease, recurring symptoms can be controlled using an on-demand regimen of 20 mg once daily when required.
- For long-term management and prevention of relapse in gastro-oesophageal reflux disease (GORD).
- For the prevention of gastroduodenal lesions and dyspeptic symptoms induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk, and with a need for continuous NSAID treatment.

PRAZOLOC 40 is indicated in the following:

- For the short-term treatment of duodenal ulcer.
- Gastric ulcer.
- Reflux oesophagitis.
- For the treatment of Zollinger-Ellison Syndrome.

CONTRAINDICATIONS

PRAZOLOC is contraindicated in the following:

- Hypersensitivity to pantoprazole or to any of the other ingredients of **PRAZOLOC**.
- Severe impairment of liver function.

- Safety and efficacy in children have not been established.
- Co-administration with atazanavir and nelfinavir (see **INTERACTIONS**).

WARNINGS AND SPECIAL PRECAUTIONS

PRAZOLOC is not indicated for mild gastro-intestinal complaints such as nervous dyspepsia.

Prior to treatment the possibility of malignancy of gastric ulcer or a malignant disease of the oesophagus should be excluded, as the treatment with **PRAZOLOC** may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

Use of **PRAZOLOC 20** as preventative of gastroduodenal ulcers, induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued NSAID treatment and have an increased risk to develop gastro-intestinal complications.

Daily treatment with any acid-blocking medicines over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin caused by hypo- or achlorhydria. Rare cases of cyanocobalamin deficiency under acid-blocking therapy have been reported in the literature. This should be considered when respective clinical symptoms are observed.

In the case of a rise of the liver enzymes, **PRAZOLOC** should be discontinued.

Diagnosis of reflux oesophagitis should be confirmed by endoscopy.

Tubulointerstitial nephritis:

The risk of tubulointerstitial nephritis leading to chronic renal inflammation and reduced renal function is associated with the use of PPIs. Tubulointerstitial nephritis may progress to renal failure as it is not necessarily reversed when treatment is discontinued (see **SIDE EFFECTS**).

Effects on the ability to drive and use machines:

PRAZOLOC may cause dizziness, disturbances in vision, somnolence or vertigo. Patients should be advised to refrain from operating machinery or driving, until they know how **PRAZOLOC** affects them.

Maltitol:

Patients with the rare hereditary condition of maltitol intolerance should not take **PRAZOLOC.**

INTERACTIONS

Pantoprazole decreases the concentrations of atazanavir and nelfinavir. Co-administration of **PRAZOLOC** and atazanavir or nelfinavir is contraindicated (see **CONTRAINDICATIONS**).

PRAZOLOC is metabolised by the cytochrome P450 system, primarily by isoenzyme CYP2C19, and may alter the metabolism of some medicines metabolised by these enzymes.

No clinically significant interactions were, however, observed in specific tests with a number of such medicines or compounds, namely antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, warfarin and oral contraceptives. However, the response to anticoagulants such as warfarin, may be affected by **PRAZOLOC**. It is therefore good practice to monitor the patient with additional PT (prothrombin time) / INR (international normalised ratio) determinations when **PRAZOLOC** is initiated, discontinued or taken irregularly.

Changes in absorption should be observed when medicines whose absorption is pH-dependent, e.g. ketoconazole, are taken concomitantly.

There are no interactions with concomitantly administered antacids.

Concomitant intake of food has no influence on the bioavailability of **PRAZOLOC**.

HUMAN REPRODUCTION

The use of **PRAZOLOC** in pregnancy and lactation is not recommended as safety and efficacy have not been established.

DOSAGE AND DIRECTIONS FOR USE

PRAZOLOC should be taken preferably in the morning. **PRAZOLOC** may be taken with food or on an empty stomach.

PRAZOLOC should be swallowed whole with a little water either before or during breakfast. Do not crush, break, or chew the tablet.

Duodenal ulcer:

The recommended oral dose is **PRAZOLOC 40** once daily. The total treatment with oral **PRAZOLOC** should be 2 to 4 weeks. If the duodenal ulcer has been demonstrated to be associated with *Helicobacter pylori* infection, **PRAZOLOC** should be used in combination with appropriate antibiotics.

Gastric ulcer:

The recommended oral dose is **PRAZOLOC 40** once daily for 4 to 8 weeks. In the case of suspected gastric ulcer, malignancy of the gastric ulcer should be excluded, as treatment could conceal the symptoms and may delay diagnosis.

Reflux oesophagitis:

The recommended oral dose is **PRAZOLOC 40** once daily for 4 to 8 weeks.

Zollinger-Ellison Syndrome:

For management of Zollinger-Ellison Syndrome patients should start their treatment with a daily dose of **80 mg** (**2 tablets of PRAZOLOC 40)**. Thereafter, the dosage can be titrated up or down as needed using measurements of gastric acid secretion as a guide. With doses above 80 mg daily, the dose should be divided and given twice daily.

Mild gastro-oesophageal reflux disease (GORD):

The recommended oral dose is **PRAZOLOC 20** per day. A 4 week period is usually required for healing of mild (GORD). If this is not sufficient, healing will usually be achieved within a further 4 weeks. In patients with healed reflux disease, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily when required.

If symptom control has not been achieved after four weeks of treatment with the prescribed daily dose, further investigation is recommended.

Long-term management and prevention of relapse in gastro-oesophageal reflux disease (GORD):

For long-term management a maintenance dose of one **PRAZOLOC 20** tablet per day is recommended, increasing to **PRAZOLOC 40** per day if a relapse occurs. After healing of the relapse, the dose can be reduced to **PRAZOLOC 20**. Experience with long-term administration is limited.

If symptom control has not been achieved after four weeks of treatment with the prescribed daily dose, further investigation is recommended.

For prevention of gastro-duodenal lesions and dyspeptic symptoms induced by non-selective non-steroidal anti-inflammatory drugs (NSAID's) in patients at risk and with a need for continuous NSAID treatment.
The recommended oral dose is one **PRAZOLOC 20** per day.

Elderly patients:

No dosage adjustment is necessary in the elderly.

Impaired renal function:

No dosage adjustment is required in the presence of impaired renal function.

Impaired liver function:

A daily dose of **PRAZOLOC 20** should not be exceeded in patients with mild to moderate liver impairment (see **Pharmacokinetic properties** and **WARNINGS AND SPECIAL PRECAUTIONS**). Doses of **PRAZOLOC** may need to be reduced in patients with hepatic impairment.

SIDE EFFECTS

The following side effects may occur:

Infections and infestations:

Frequent: Gastro-intestinal infection.

Blood and lymphatic system disorders:

Less frequent: Thrombocytopenia, leukopenia, agranulocytosis.

Immune system disorders:

Less frequent: Anaphylactic reactions including anaphylactic shock, angioedema.

Metabolism and nutrition disorders:

Less frequent: Elevated triglycerides and increased body temperature.

Psychiatric disorders:

Frequent: Insomnia.

Less frequent: Mental depression, reversible confusional state, agitation, hallucinations, somnolence.

Nervous system disorders:

Frequent: Headache.

Less frequent: Dizziness, paraesthesia.

Eye disorders:

Less frequent: Disturbances in vision (blurred vision), anterior ischaemic optic neuropathy.

Ear and labyrinth disorders:

Less frequent: Vertigo, tinnitus.

Vascular disorders:

Less frequent: Peripheral oedema.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Dyspnoea, bronchospasm.

Gastro-intestinal disorders:

Frequent: Constipation or flatulence, diarrhoea, upper abdominal pain.

Less frequent: Vomiting, nausea, dry mouth, stomatitis, taste disturbances.

Hepatobiliary disorders:

Less frequent: Severe hepatocellular damage leading to jaundice with or without hepatic failure, increased liver enzymes (transaminases, γ-GT), hepatitis, hepatic encephalopathy.

Skin and subcutaneous tissue disorders:

Less frequent: Allergic reactions such as pruritus, and skin rash, urticaria, severe skin reactions, such as Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis (Lyell-syndrome) and photosensitivity.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Arthralgia, myalgia.

Renal and urinary system disorders:

Less frequent: Difficulty in urinating, increased frequency and volume of urination, painful urination, and interstitial nephritis with possible progression to renal failure as it is not necessarily reversed when treatment is discontinued. (See **WARNINGS AND SPECIAL PRECAUTIONS**).

Reproductive system and breast disorders:

Less frequent: Impotence, gynaecomastia.

General disorders and administrative site conditions:

Frequent: Fatigue.

Less frequent: Increased sweating, malaise.

Post-marketing exposure:

Frequency unknown: Interstitial nephritis with possible progression to renal failure as it is not necessarily reversed when treatment is discontinued.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

No specific therapeutic recommendation can be made in cases of overdosage. There are no known symptoms of overdosage.

IDENTIFICATION

PRAZOLOC 20: Yellow coloured, capsule shaped, biconvex tablet plain on both sides.

PRAZOLOC 40: Yellow coloured, capsule shaped, biconvex tablet with “40” imprinting on one side and plain on the other side.

PRESENTATION

PRAZOLOC 20: Aluminium foil blister strip of 10 tablets packed in a carton as 10’s and 30’s.

PRAZOLOC 40: Aluminium foil blister strip of 10 tablets packed in a carton as 30’s.

STORAGE INSTRUCTIONS

Store at or below 25 °C. Protect from light.

STORE THIS MEDICINE OUT OF REACH OF CHILDREN.

Keep the blisters in the outer carton until required for use.

REGISTRATION NUMBERS

PRAZOLOC 20: 43/11.4.3/1147

PRAZOLOC 40: 43/11.4.3/1148

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION

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